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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/640,780	08/18/2000	Jacques Dumas	BAYER8C1	7350

23599 7590 10/20/2004

MILLEN, WHITE, ZELANO & BRANIGAN, P.C.
2200 CLARENDON BLVD.
SUITE 1400
ARLINGTON, VA 22201

EXAMINER	
ROBINSON, BINTA M	

ART UNIT	PAPER NUMBER
1625	

DATE MAILED: 10/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/640,780	DUMAS ET AL.	
	Examiner	Art Unit	
	Binta M Robinson	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1,9,11-13,15,16,37,41-43,46,80 and 81 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1, 9, 11, 12, 13, 15, 16, 37, 41, 42, 43, 46, 80, and 81 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

The elected group drawn to the compound of formula I wherein A is oxazole, B is carbocyclic ring substituted with a pyridinyloxy moiety, and a method for the treatment of cancerous cell growth is modified to be drawn to the compounds of formula I wherein A is isoxazole, B is a phenyl ring substituted by Y-Ar, Y is O or S, Ar is phenyl or pyridiny, optionally substituted as claimed, R^1 is as claimed, Rc is as claimed, R^5 and $R^{5'}$ are as claimed. This group is drawn to claims 1, 9, 11, 12, 13, 15, 16, 37, 41, 42, 43, 46, 80, and 81. The restriction is made FINAL.

The nonstatutory double patenting rejection of claims 1, 9, 11, 12, 13, 15, and 16 made at paper no. 26 are withdrawn in light of applicant's comments in the amendment filed 8/24/04.

The applicants' traverse the 112, first paragraph rejection made at paper no. 26 alleging that there is adequate disclosure within the specification, accompanied by guidance provided by the example, for one skilled in the art to make the compounds recited in the claims and to use them in accordance with the methods defined without undue experimentation and that no evidence has been presented to the contrary. However, specific experimental data for the effect of the claimed compounds on cancerous cell growth is not disclosed. On page 2, lines 12-14 of the specification, it is stated that the compounds of the invention are useful in treating solid cancers such as lung, pancreas, thyroid, bladder, or myeloid leukemia. However, while pancreatic cancer, acute myeloid leukemia, and colorectal cancer are highly associated with the

ras/raf kinase pathway, while bladder cancer is associated with the ras/raf kinase pathway to an intermediate extent, small-cell lung carcinoma is not highly correlative with the raf kinase pathway as indicated by the fact that there have only been discovered a low frequency of ras oncongene mutations in small-cell lung carcinoma. See Table 10.2 page 89 of Lemoine et. al.

(modified rejections)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 9,11,12, 13,15,16, 37, 41-43, 46, 80, and 81 are rejected under 35 U.S.C. 112, first paragraph, because the specification, does not reasonably provide enablement for a method of treating all cancerous cell growth with a compound of formula I found in claim 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have need described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

The nature of the invention

The nature of the invention is the treatment of all cancerous cell growth with the compounds of formula (I) as found in claim 1.

The state of the prior art and the predictability or lack thereof in the art

The state of the prior art is that cancer therapy remains highly unpredictable. The various types of cancers have different causative agents, involve different cellular mechanisms, and consequently, differ in treatment protocol. There are different cellular mechanisms, the unpredictability in the art and the different treatment protocols for the various types of cancers. Raf Kinase is but one pathway by which some cancers are mediated. Raf kinase activity and its inhibition have been correlated with a variety of human tumor types. See line 35 of page 1 of the specification. Raf Kinase acts downstream of Ras and is an effector of Ras. See page 447 of Sternberg et. al. Activation of RAS results in the recruitment of RAF to the plasma membrane where it is activated. See page 447 of Sternberg et. al. All cancers are not caused by the raf/ras pathway. While some cancers are traceable to high Ras mutations, which in term affect Raf functioning, such as colorectal cancer, some other cancers, such as small-cell lung carcinoma have only been associated with low frequency mutations in Ras. See page 89 of Lemoine et. al.

The amount of direction or guidance present and the presence or absence of working examples

The only direction or guidance present in the instant specification is found on pages 112-114 which discloses the raf Kinase assays of the compounds. Specific experimental data for the effect of the claimed compounds on cancerous cell growth is not disclosed. On page 2, lines 12-14 of the specification, it is stated that the

compounds of the invention are useful in treating solid cancers such as lung, pancreas, thyroid, bladder, or myeloid leukemia. However, while pancreatic cancer, acute myeloid leukemia, and colorectal cancer are highly associated with the ras/raf kinase pathway, while bladder cancer is associated with the ras/raf kinase pathway to an intermediate extent, small-cell lung carcinoma is not highly correlative with the raf kinase pathway as indicated by the fact that there have only been discovered a low frequency of ras oncongene mutations in small-cell lung carcinoma. See Table 10.2 page 89 of Lemoine et. al.

The breadth of the claims

The breadth of the claims is the treatment of all cancerous cell growth with the compounds of formula I in claim 1.

The quantity of experimentation needed

The quantity of experimentation needed would be undue when faced with the lack of direction and guidance present in the instant specification in regards to the treatment of all cancerous cell growth regardless of whether or not the cancer is mediated by the raf kinase pathway and when faced with the unpredictability of the cancer therapy art.

The level of the skill in the art

Even though the level of skill in the cancer therapy art is very high, based on the unpredictable nature of the invention and state of the prior art and the extreme breadth of the claims and lack of guidance and direction for the treatment of all cancerous cell growth, one skilled in the art could not use the claimed invention without undue experimentation.

In terms of the 8th Wands factors, undue experimentation would be required to make or use the invention based on the content of the disclosure due to the breadth of the claims, the level of predictability in the art of the invention, and the poor amount of direction provided by the inventor. Taking the above factors into consideration, it is not seen where the instant claim is enabled by the instant application.

(new rejections and objections)

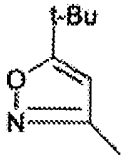
The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1, 37, 43, and 81 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. In claim 1, line 5 and everywhere else throughout claims 1, claim 37, claim 43, and 81 the phrase "up to per-halosubstitution" is indefinite. It is not clear what this range is encompassing and what the lower limit or boundary of this range is.

The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: The proviso in claims 1, 9, 11, 12, 13, 15, 16, 80, and 81 does not have proper antecedent basis in the specification. The proviso that where A is



, B is not

wherein n = 2-4,

is not disclosed anywhere in the specification.

The IDS filed 6/29/01 has been considered.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Binta M. Robinson whose telephone number is (571) 272-0692. The examiner can normally be reached on M-F (9:30-6:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562.

A facsimile center has been established. The hours of operation are Monday through Friday, 8:45 AM to 4:45 PM. The telecopier numbers for accessing the facsimile machine are (703)308-4242, (703)305-3592, and (703)305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)-272-1600.

BMR
September 30, 2004

Cecilia J. Tsang
Supervisory Patent Examiner
Technology Center 1600